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IN THE

Supreme Court of the United States

October Term, 1965

No. 595

FERNANDA MISANI,

Plaintiff-Appellant,

v.

ORTHO PHARMACEUTICAL CORPORATION, a New Jersey corporation, Johnson & Johnson, a New Jersey corporation, Robert Johnson, Harry McKenzie, Berton Todd, Evan Spalt, John Friebely, and William Oroshnik,

Defendants-Respondents,

ON APPEAL FROM THE SUPREME COURT OF NEW JERSEY

JURISDICTIONAL STATEMENT

FERNANDA MISANI,
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Westfield, New Jersey

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In the

SUPREME COURT OF THE UNITED STATES

October Term 1965

No. _____

Fernanda Misani,

Plaintiff-Appellant,

vs.

Ortho Pharmaceutical Corporation, a New Jersey corporation, Johnson & Johnson, a New Jersey corporation, Robert Johnson, Harry McKenzie, Berton Todd, Evan Spalt, John Friebely, and William Oroshnik,

Defendants-Respondents,

ON APPEAL FROM THE SUPREME COURT OF NEW JERSEY

Jurisdictional Statement

Appellant appeals from the judgment of the Supreme Court of New Jersey dated June 1, 1965 (Appendix A)

which reversed the judgment of the Appellate Division of New Jersey, in favor of the appellant, dated March 11, 1964. The order of the Supreme Court of New Jersey was made final on July 1, 1965, by denial of the petition for rehearing (Appendix A). A notice of appeal was filed with the Clerk of the Supreme Court of New Jersey on August 24, 1965.

Appellant submits this statement to show that the Supreme Court of the United States has jurisdiction of the appeal and that substantial questions are presented.

A. Opinions Below in the First and Second Action.

This is the second action in a nine-year litigation between the same parties. At each stage of the litigation, appellant, plaintiff below, has sought consolidation of the two cases, but it has been denied. The defendants-respondents are Johnson & Johnson, a corporation of New Jersey, Ortho Pharmaceutical Corporation, a totally-owned subsidiary, Robert Johnson, Chairman of the Board, Harry McKenzie, President of Ortho, Berton Todd, Vice-President in charge of Research, Evan Spalt, Vice-President, John Friebely, Director of Personnel, and William Oroshnik, who had an administrative position in the Organic Division.

For the sake of brevity, reference to the respondents will be made hereinafter as "Johnson & Johnson," since the parent company, through a maze of some eighty domestic and foreign subsidiaries, has controlled the business enterprise, and through its legal and patent staff, has directed and handled all phases of the patent matters which are in issue in this case.

a. Opinions below in the first case.

The Trial Court's opinion, dated May 1, 1961, which dismissed plaintiff's case, and the Appellate Division's affirmance, of May 19, 1962, were not published. Petition for certification to the Supreme Court of New Jersey was denied on September 17, 1962. 38 N.J. 304 (1962). Motion for consolidation of the two

cases was again denied on December 11, 1962. On April 1, 1963, the United States Supreme Court denied certiorari. 372 U.S. 959 (1963) (Docket No. 819, Fall Term, 1962). Nine copies of that petition with the opinion of the trial court annexed thereto, are submitted together with this Jurisdictional Statement. The disposition of the causes of action in the first case is relevant to determine the extent of res judicata (Question 8 involved in this appeal).

b. Opinions in the second case.

The opinion of the Supreme Court of New Jersey, dated June 1, 1965 is published at 44 N.J. 552; 210 A.2d 609 (1965) and is set forth in Appendix B. The opinion of the Appellate Division, which reversed the trial court and remanded for trial, is published at 83 N.J. Super. 1; 198 A.2d 791 (1964) and is set forth in Appendix C.

B. How the Federal Questions Were Raised.

The constitutional questions involved were properly raised in the trial court, as early as the complaint, and later the pretrial order, request to charge the jury, exception to the Court's charge, argued in all briefs on appeal, Petition for Rehearing, and expressly passed on by the New Jersey courts. After the decision of the Appellate Division in 1964, both parties appealed to the Supreme Court of New Jersey, because of the importance of the federal questions presented.* Since this proceeding draws into question the constitutionality of 35 U.S.C. 101, 102(c), 112, 135, 154, 251, 253 and the applicability of U.S. Constitution, Art. VI, and neither the United States, nor any agency, officer or employee, is a party, it is noted that 28 U.S.C. 2403 may be applicable.

* A certificate of federal questions by the New Jersey Supreme Court has been requested and will be made part of the record as soon as received.

C. Statement of the Grounds on Which the Jurisdiction of this Court is invoked.

(i) The jurisdiction of this Court is founded upon the invalidation of federal law by the New Jersey courts, in a field of federal pre-emption. 28 U.S.C. 1257 (1). In addition, all the questions, including question 8, are sufficiently substantial and important, each in itself, to warrant grant of certiorari. 28 U.S.C. 2103. Briefs and appendixes before the Supreme Court of New Jersey are duly certified and separately presented.

(ii) The texts of the constitutional, statutory provisions, Rules of the United States Patent Office and Excerpts from the Manual of Patent Examining Procedure, U.S. Department of Commerce (1961), involved here, are set forth in Appendix D.

(iii) Appellant is the holder of a degree of Doctor of Philosophy in Organic Chemistry, and an advanced expert in the field of medicinal chemistry (Appendix C, 10a, 25a). In January 1955, she was employed by the respondents with the rank of senior research associate. In April 1956, she was summarily discharged, without notice nor hearing, under the accusation of "incompetency." Johnson & Johnson, Ortho Pharmaceutical Corporation and the individual respondents, circulated, orally and in writing, that her work was no good, deprecated and concealed her inventions, and made it impossible for her to obtain other employment in her field.* The first action was instituted in April 1957 for breach of the contract of employment, fraud at the hiring and defamation. The disposition of the causes of action in

* Appellant has now completed Law School, passed Bar Examinations, and is admitted to practice before the United States Patent Office.

the first case is summarized in Point F (4) of this Jurisdictional Statement, and in the Petition for Certiorari, Docket No. 819, Fall Term, 1962.

During her employment, appellant invented the novel chemical compound "4-methyl 4-phenyl 5-pyrazolone." Three days after the substance had exhibited outstanding value in the treatment of convulsions, she was discharged. In 1959, during the pendency of the first case, respondents secured Letters Patent U.S.P. 2,878,263 which describes in detail the same chemical compound, the novel process of manufacture of the compound and its novel use as a cure against convulsions. The patent designates William Oroshnik, one of the respondents, as inventor. It is shown at page 14, infra.

In 1963, during the pendency of the appeal in this second case, before the Appellate Division of New Jersey, appellant secured, in her name, Letters Patent U.S.P. 3,079,397. Recently, in January 1965, during the pendency of the appeal before the Supreme Court of New Jersey, she secured Letters Patent U.S.P. 3,166,475. The latter issued from a divisional application of the former. The two patents are shown at page 16 and 19, infra. Apart from the technicalities of the language of the claims, the two patents, manifestly, cover the identical subject matter of U.S.P. 2,878,263, which issued in 1959. These two patents, which appellant has obtained in her name, must, under the decisions of the New Jersey courts, now be assigned to Johnson & Johnson. It will be demonstrated infra (page 11) that the two patents were not issued by inadvertence by the United States Patent Office, but with knowledge of the pending litigation and after an interference proceeding with the patent issued in Oroshnik's name.

In September 1959, appellant moved to file a supplemental complaint, in the first case. The motion was denied, on the ground that the two cases were totally different. This second action, instituted in March 1960, sought: 1) an adjudication that respondents had no proprietary rights on the invention, and 2) damages for deprivation of intellectual credit. The complaint alleged wilful and malicious concealment of the invention and fraud on the United States Patent Office for obtaining a patent in the name of one who was not the real inventor.

Trial occurred in April 1962. Appellant's request of a special verdict with written interrogatories to be submitted to the jury, was denied (R213a). The jury rendered a general verdict of no cause of action. On March 11, 1964, the Appellate Division, reversed and remanded the case for trial as to Johnson & Johnson, Ortho and Oroshnik (Appendix C, 41a). On June 1, 1965, the Supreme Court of New Jersey reversed the Appellate Division.

The position of the New Jersey courts on the constitutional questions involved, is:

a) On the matter of ownership, the New Jersey courts compel appellant to assign to Johnson & Johnson her two patents, U.S.P. 3,079,397 and U.S.P. 3,166,475, which issued in 1963 and 1965 respectively, that is, some four and six years after U.S.P. 2,878,263. Appellant's argument that assignment of the two patents violates 35 U.S.C. 154, by rewarding Johnson & Johnson with an extension of the seventeen-year monopoly for the same invention, has been held "frivolous." (Appendix C at 15a; Appendix B at 3a.)

b) On the matter of willful concealment, delay in filing the patent application and deprecation of the invention, during the pendency of the first case, for malicious motives, at a time when respondents wished to represent the appellant as an "incompetent" chemist, the New Jersey courts hold, as a matter of law, that the employer has the absolute right to conceal employees' inventions, even "scrap" them and later seek patent rights (Appendix B at 3a). This holding is repugnant to our constitutional policy, and invalidates 35 U.S.C. 102 (c), as construed by this Court. Electric Battery Co. v. Shimadzu, 307 U.S. 5, 15.

c) With respect to the deprivation of intellectual credit and fraud on the United States Patent Office, the trial judge, after deciding in favor of the employer on the matter of ownership, has held that a scientist, who has agreed to assign proprietary rights to the employer, "forfeits" the right to have his or her name as the inventor, on the patent (R99a; R115a). The Appellate Division reversed (Appendix C, 16a). The Supreme Court of New Jersey, however, has reinstated the judgment of the trial court and holds that it is proper for an employer to obtain a patent in the name of one employee on subject matter invented by another employee. It relieves Johnson & Johnson of liability merely because "the patent claim (one line) was carefully limited to the compound itself" (Appendix B at 7a). Appellant submits that this holding expressly invalidates 35 U.S.C. 101, 112 and 154.

d) The New Jersey courts have permitted Johnson & Johnson, in an action for deprivation of intellectual credit, to argue that U.S.P. 2,878,263

is invalid and appellant was not deprived of credit for something worthless (Appendix C at 9a, 13a, 15a, 28a; Appendix B, at 5a). Appellant's argument that Johnson & Johnson has retained its full monopoly, has enjoyed the benefit of the patent and is estopped to deny the validity, has been rejected.

The New Jersey courts have expressly refused to follow substantive rules of the United States Patent Office in a field of federal pre-emption (Appendix C at 34a). Application of 37 C.F.R. 1.216 (a)(4) (Appendix D) would have excluded the testimony of respondent Oroshnik as to his alleged conception of idea of making the substance and would have entitled appellant to judgment, as a matter of law. Oroshnik had no proof whatsoever that he conceived the idea of making the compound, no exhibits and no witnesses. Appellant's testimony, on the other hand, was fully corroborated by authentic exhibits. The motion for judgment has been denied.

(iv) Cases sustaining the jurisdiction of this Court are:

Flournoy v. Wiener, 321 U.S. 253.

Bryant v. Zimmerman, 278 U.S. 63.

Anonymous v. Baker, 360 U.S. 287.

Beecher v. Contour Laboratories, 279 U.S. 388.

Sears, Roebuck & Co. v. Stiffel Company, 376 U.S. 225.

United States v. American Bell Telephone Co., 128 U.S. 315.

Woodbridge v. United States, 263 U.S. 50.

Dalzell v. Dueber Watch Case Manufacturing Co., 149 U.S. 315.

United States v. Dubilier Condenser Corp., 289 U.S. 178.

Sperry v. Florida, 373 U.S. 379.

D. Questions Presented by the Appeal.

The following questions are presented by this appeal:

1. Where the Constitution of the United States (Article I, Sec. 8, Clause 8) grants to Congress the power to promote the progress of science and useful arts, by rewarding authors and inventors with a monopoly "for limited times," and 35 U.S.C. 154 sets the limit at seventeen years, and where the former employer, in 1959, obtained U.S.P. 2,878,263 by fraud on the Patent Office, in the name of one who was not the inventor, and has enjoyed a monopoly under it since 1959, and the Patent Office properly issued in 1963 U.S.P. 3,079,397 and in 1965 U.S.P. 3,166,475 to the real inventor-former employee appellant here, which cover the identical subject matter of U.S.P. 2,878,263, may the New Jersey courts compel assignment of the two later-issued patents to the former employer, where the net result is to extend the monopoly for the employer beyond the seventeen-year period?

2. May an employer conceal inventions of an employee, and even "scrap" them, as the New Jersey

courts have held, and then, long time afterwards, obtain a patent, deliberately, in the name of one who is not the real inventor?

3. Where a novel process produces a novel product and the product cannot be made by any other process and the product has only one use, in curing a serious disease, do product, process and use constitute a single invention and does the holding of the New Jersey Supreme Court that the claim on the product does not include the process and use, repeal 35 U.S.C. 101, 112 and 154?

4. Where Congress has set up an agency, the Board of Interferences in the United States Patent Office, for the adjudication of inventorship between two contesting parties, and an interference proceeding was instituted, and the Patent Office had no power to compel the patentee to correct certain errors in U.S.P. 2,878,263 to continue the interference, is the holding of the New Jersey courts that the employer-patentee had no duty to correct the errors, repugnant to federal law?

5. Where Congress, by the reissue provisions 35 U.S.C. 251, permits a patentee to correct errors in an issued patent, and the error of U.S.P. 2,878,263 consisted of claiming too broad a monopoly, is the holding of the New Jersey courts that the employer had no duty to narrow the monopoly, repugnant to federal law?

6. Where Congress has enacted the disclaimer provisions, 35 U.S.C. 253, is the employer-patentee, who has continued to assert the full monopoly under U.S.P. 2,878,263, estopped from asserting its invalidity?

7. Does the holding of the New Jersey courts that they are not bound by the rules of the United States Patent Office, violate the Supremacy Clause, U.S. Const., Art. VI?

8. Is the contract as presently enforced against appellant, unconstitutional, and does the application of the doctrine of res judicata in this second case, constitute denial of due process of law?

E. Statement of the Case: The Proceeding in the United States Patent Office.

In December 1959, within one year from the issuance of the patent in Oroshnik's name, as provided by U.S.C. 135, appellant filed a patent application in her name and requested the institution of an interference proceeding with U.S.P. 2,878,263. In compliance with the rule of the United States Patent Office, 37 C.F.R. 1.205, (Appendix D) which controls interferences between an application and an issued patent, she copied the single claim, the broad product claim of U.S.P. 2,878,263, as worded. In addition, she included in her application, narrower claims, covering the novel process of manufacture of the substance and the novel use, as an anticonvulsant.

On May 5, 1960, the United States Patent Office instituted the interference and pursuant to the provision of Manual of Patent Examining Procedure, U.S. Department of Commerce (1961) Sec. 1102.01(b) (Appendix D), notified appellant that, should she lose in the contest with respect to the product claim in issue, the remaining claims in her application would be rejected. The reason was that they were "unpatentable over" the product claim, because integral with the same invention as the product.

In January 1961, the Patent Office notified the parties that the interference, based on the product claim, as worded, would be dissolved, because it claimed a too broad monopoly. The Examiner had discovered a reference, in Beilstein, which anticipated the name and formula of the compound, "a type formula" (R282a; Appendix C at 13a, 19a) but did not anticipate the compound itself. No one had made the substance, no one knew how to make it, nor, obviously, tested the substance or discovered the novel use as an anticonvulsant. Appellant, in reliance on the reissue provisions, 35 U.S.C. 251, which permit a patentee to correct errors in an issued patent and narrow the scope of the monopoly, moved that Johnson & Johnson substitute a narrower claim on the use of the substance as an anticonvulsant, as described in the specification (R211a). Narrowing the scope of the product claim was essential, at that stage, to continue the interference to an adjudication of inventorship.

Johnson & Johnson, however, took advantage of its patentee status and refused to narrow the monopoly.* The United States Patent Office has no jurisdiction to compel a patentee to correct errors and in June 1961 the interference was dissolved, with no adjudication of inventorship (R210a).

Crucial to the questions involved in this appeal, is that, after the interference proceeding, Johnson & Johnson has continued to enjoy the broad monopoly of the product claim and has not disclaimed the patent, as provided by 35 U.S.C. 253.

* The legal staff of Johnson & Johnson has essentially admitted that they would have lost the interference proceeding. Rule of the United States Patent Office, 37 C.F.R. 1.216(a)(4), would have excluded the testimony of respondent Oroshnik as to his alleged conception of idea of making the compound, because totally uncorroborated. This topic is discussed below at p. 35 of this Jurisdictional Statement.

After the dissolution of the interference, the United States Patent Office withdrew the earlier rejection of process and use claims, and in due course, issued the two patents, U.S.P. 3,079,397 and U.S.P. 3,166,475, in appellant's name. Manifestly the two patents issued because a conflict of interest had been established between appellant and Johnson & Johnson. 35 U.S.C. 135 (Appendix D) provides for the issuance of a second patent for the same invention to a party other than the first patentee, after an interference proceeding. The two patents would not have issued to Johnson & Johnson, because it would have resulted in an extension of the monopoly, "double patenting." In re Dunbar, 278 F.334 (D.C. Cir. 1922); In re Fischel, 136 F.2d 254, 258 (C.C.P.A. 1943); Application of Hession, 296 F.2d 930, 935 (C.C.P.A. 1961).

The two patents, shown at page 16 and 19, cover the identical subject matter of U.S.P. 2,878,263. The compound, 4-methyl 4-phenyl 5-pyrazolone, can only be manufactured by the novel process which is described in detail in U.S.P. 2,878,263. (Compare U.S.P. 2,878,263, Example 1 in Column 2, with U.S.P. 3,079,397, Column 3, lines 45 et seq., Example 2, and Claim 1). The same use, as an anticonvulsant, is described in U.S.F. 2,878,263 and in U.S.P. 3,166,475, Column 3, line 68 to Column 5, line 27. Product, process and use, in this case, constitute a single invention, the making of a novel substance which has utility as a cure against convulsions.

United States Patent No. 2,878,263

EXHIBIT P17 EV. 10. MAR 1961 R. BURSTEIN

P24 EV 4/2/63 JH3

EXHIBIT P4 EV DEC 1960 R. BURSTEIN, C. S. R.

United States Patent Office

2,878,263

Patented Mar. 17, 1959

2,878,263

4-METHYL-4-PHENYL-5-PYRAZOLONE

William Orochnik, Plainfield, N. J., assignor to Ortho Pharmaceutical Corporation, a corporation of New Jersey

No Drawing. Application February 14, 1958
Serial No. 715,210

1 Claim. (Cl. 260—310)

This invention relates to 4-methyl-4-phenyl-5-pyrazolone. The novel compound possesses particular value as an anti-convulsant and is useful in the treatment of epilepsy.

Epilepsy has been defined as a cerebral dysrhythmia which may or may not be accompanied by loss of consciousness and body movements. It is now known that epileptic convulsions are related to the flow of electricity from neurons of the cerebral cortex. The type of chemical reaction which is responsible for these cerebral neuronal discharges is not known, but generally, convulsions and loss of consciousness are characterized by abnormally fast brain waves. When the patient suffers loss of consciousness and convulsions, the seizures are referred to as grand mal, a form of major epilepsy. However, convulsions do not necessarily accompany epilepsy, and in some instances consciousness is not lost. When the patient loses consciousness but convulsions are not observed, the attacks are known as petit mal. A third type of epilepsy has been clinically classified as psychomotor epilepsy.

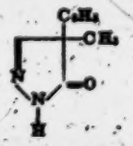
Many drugs are known which reduce or diminish epileptic seizures in man. In general, those drugs which will act as depressants of nervous transmission are effective for this purpose. The hypnotics, such as barbiturates, are effective in doses sufficient to produce anesthesia. Phenobarbital is one of the better anti-convulsants, but must be administered in hypnotic doses. The related hydantoins and oxazolidinediones have also been found to possess anti-convulsant properties. Such drugs, however, interfere to a greater or lesser extent with the normal activities of the patient.

It is most important, that any drug which is used as an anti-convulsant have very low toxicity since the nature of epilepsy requires that the patient use the drug daily and over a long period of time. The ideal anti-convulsant drug should be non-toxic, well tolerated, long acting, and devoid of sedative effects.

It is an object of this invention to provide a new compound, 4-methyl-4-phenyl-5-pyrazolone, which has a high protective index and is non-toxic in use over a long period of time.

Still another object of this invention is to provide a new compound for use in the treatment of epilepsy.

The present invention is particularly concerned with the compound 4-methyl-4-phenyl-5-pyrazolone having the structure



It has been found that the aforesaid compound has unexpected and unobvious properties of great value in combating epilepsy. This compound may take the form of tablets, powders, capsules, or other dosage forms

which will be particularly useful for oral ingestion. The active material, namely the 4-methyl-4-phenyl-5-pyrazolone, may be admixed with solid diluents and/or tableting adjuvants such as corn starch, sucrose, lactose, magnesium stearate, talc, aluminum hydroxide, calcium carbonate; gums such as acacia, or the like. Any of the tableting materials used in pharmaceutical practice may be employed where there is no incompatibility with the 4-methyl-4-phenyl-5-pyrazolone. The material may be placed in a gelatin capsule and administered in that form. Alternatively, the compound may be emulsified in a liquid in which it is not soluble.

Anti-convulsant drugs may be assayed in the laboratory by the minimum electro-shock method. In this procedure, the drug is administered orally to the animals under test. After one hour, the animal is subjected to the direct-current stimulus that is approximately equal to three times the current necessary to produce maximum seizures. The effectiveness of various 3- and 4-substituted-5-pyrazolones as anti-convulsants is summarized in Table I. In this table, the first column gives the effective dose in milligrams per kilogram required to prevent convulsions in one-half of the animals subjected to the minimum electro-shock procedure. The second column indicates the amount of drug in milligrams per kilogram that produced neurological toxic symptoms in one-half of the experimental group. The third column of this table reports the amount of drug, again in milligrams per kilogram, that was fatal to fifty percent of the test group. Column 4 indicates the protective index (N. T. S_{50}÷ED_{50}).

TABLE I

	ED_{50}	NTS_{50}	LD_{50}	P.I.
3-undecyl	800+		1,000	
3-dodecyl	800+		1,000	
4-dodecyl	800+		1,000	
4,4-dimethyl	800+		800	
4,4-dibutyl	<1,000	800		
4-phenyl-4-methyl	80	167		2.1

It will be noted that only a single member of the group investigated had a useful protective index.

Example I

4-METHYL-4-PHENYL-5-PYRAZOLONE

A solution of 4.3 grams (0.021 mole) of ethyl-α-formyl-α-methylphenylacetate, 8.4 milliliters of acetic acid and 3.6 grams of 85% hydrazine hydrate in 300 milliliters of absolute ethanol is refluxed for 14 hours, with condensed ethanol being percolated through a Soxhlet thimble containing 40 grams of calcium oxide before returning to the reaction flask. The alcohol solution is filtered and concentrated under vacuum to a volume of 25 milliliters and diluted with 50 milliliters of water to cause separation of an oily solid which is leached with 300 milliliters of boiling heptane and filtered. The filtrate is evaporated to 60 milliliters to cause crystallization of a pale yellow solid which subsequently is recrystallized from an acetone-heptane mixture to yield 0.8 gram (22%) of white flakes which melted at 99–101° C. Calcd. for $C_{10}H_{10}N_2O$: N, 16.08. Found N, 15.87.

The percentage of 4-methyl-4-phenyl-5-pyrazolone in compositions for the treatment of epilepsy may be varied. It is necessary that this compound constitute a portion such that suitable dosage will be obtained. The percentage of active agent may be conveniently 10% or 25% or even 50% since activity increases with the concentration of active material. Tablets containing from

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about 25 to about 50 mg. of 4-methyl-4-phenyl-5-pyrazolone are particularly useful. The following formations are intended to be illustrative only, and may be varied or modified to a considerable extent without departing from the spirit of the invention. We do not therefore intend to limit the invention to the specific embodiments herein set forth.

Example II

	G.
Calcium carbonate	0.500
4-methyl-4-phenyl-5-pyrazolone	0.025
Calcium stearate	0.050

The 4-methyl-4-phenyl-5-pyrazolone is adsorbed onto 10% of the calcium carbonate by mixing. The remaining calcium carbonate, previously granulated with water and dried, is added to this pyrazolone mixture. The calcium stearate is then added and after mixing until uniform, the mixture is compressed into tablets.

Example III

	G.
Aluminum hydroxide	0.300
Sucrose	0.100
Lactose	0.100
Gelatin solution	0.005
4-methyl-4-phenyl-5-pyrazolone	0.050
Magnesium stearate	0.005

The 4-methyl-4-phenyl-5-pyrazolone is adsorbed onto 10% of the aluminum hydroxide with mixing. The remainder of the aluminum hydroxide is then granulated with the sucrose, lactose, and gelatin solution and dried at 50° C. These granules are then mixed with the pyrazolone aluminum hydroxide composition and magnesium stearate until uniform and compressed into tablets.

What is claimed is:

The compound 4-methyl-4-phenyl-5-pyrazolone.

No references cited.

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United States Patent Office

3,079,397
Patented Feb. 26, 1963

3,079,397

PROCESS FOR PREPARATION OF CERTAIN 4,4-DISUBSTITUTED PYRAZOLONES

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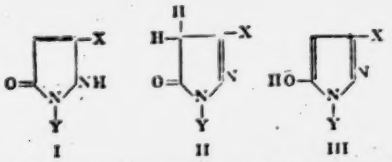
No Drawing. Filed Dec. 29, 1959, Ser. No. 862,450
2 Claims. (Cl. 260—310)

This invention relates to new compounds containing the pyrazolone nucleus and, more particularly, to 4,4-disubstituted 5-pyrazolones.

The pyrazolone nucleus has been known for a long time to exist in three tautomeric structures, and ultraviolet absorption spectra indicate that 1,3-disubstituted 5-pyrazolones may react according to the three following formulae:



I II III

Structure I is present in several substituted pyrazolones which are widely known and used as antipyretic agents. Antipyrine, tolypyrine, aminopyrine, melubrine are some of the most important members of this series. All these compounds are characterized by the presence of a phenyl group attached to the nitrogen atom in the 1-position and a methyl group in the 3-position. The 4-position is usually, but not necessarily, substituted, because for instance it is unsubstituted in antipyrine and tolypyrine. The nitrogen atom in the 2-position is substituted in antipyrine and melubrine, but it is unsubstituted in aminopyrine.

It seems reasonable to conclude that a phenyl group in the 1-position and a methyl group in the 3-position are essential for antipyretic activity, but that substitution in the 4-position is not essential.

Several 4,4-dimethyl derivatives, as well as Pyrazole Blue and Tartrazine, are derived from Formula II. The existence of structure III has been invoked to explain the products resulting from methylation with diazomethane or acylation with acid chlorides and alkali, which are O-alkyl and O-acyl derivatives. Several pyrazolone dyes are derived from structure III.

In spite of the extensive research in the field of pyrazolones, no pharmacological or clinical use has ever been reported for any compound derived from structure II, more specifically for compounds containing two substituents in the 4-position. In view of the extensive literature data in the field of pyrazolones and the absence of any physiological activity of the known pyrazolones derived from structure II, it was novel and surprising to find that compounds derived from structure II possess significant value as central depressants and more particularly as anticonvulsants.

The object of this invention is to prepare 4,4-disubstituted pyrazolones, which are unsubstituted on the two nitrogen atoms.

Another object of the invention is to describe the novel method used for the preparation of the compounds of the invention.

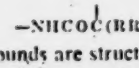
Other objects of the invention will appear from the specification and examples.

The compounds of the invention have the formula:

in which R is an alkyl group containing up to four carbon atoms, R' is an aryl group and R'' is selected from the group consisting of hydrogen and a low-molecular-weight alkyl group. It is also possible, according to the invention, that R and R' represent the same substituent.

In view of the essential features indicated above, exhibited by compounds having antipyretic activity, that is, a phenyl group on the nitrogen in the 1-position and a methyl group in the 3-position, it was also novel and unforeseeable that the anticonvulsant activity reaches the maximum value in 4-methyl-4-phenyl pyrazolone, that is, a compound which is unsubstituted both on the two nitrogen atoms and in the 3-position.

The anticonvulsant activity of the compounds of this invention may perhaps be explained by the fact that they contain the group

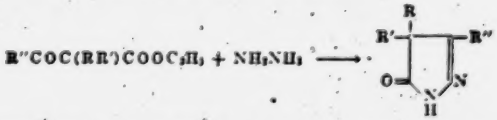


that is, these compounds are structurally related to known hypnotics and central depressants. It is not a mere coincidence that this moiety is found for instance in hydantoins, disubstituted barbiturates, oxazolidinediones, hexahydropyrimidinediones, Noludar and Doriden.

The fact that the two substituents in the 4-position of the pyrazolones of this invention are essential to physiological activity is analogous to the barbiturates where 5-unsubstituted or 5-monosubstituted barbiturates are well known to be devoid of any physiological activity. Although the mechanism of action of the compounds of the invention appears to be analogous to the known central depressants, it is to be understood that the scope of this invention is not limited by theoretical consideration of mode of action on the brain centers, mainly because such a mode of action is still little known or inadequately understood.

Anticonvulsant activity is the ability of a compound to prevent epileptic seizures, that is, convulsions accompanied by loss of consciousness, which are known as "grand mal epilepsy," and also the ability to control the milder attacks not accompanied by convulsions, known as "petit mal."

The method used for the preparation of the compounds of the invention consisted of the reaction of an α,α-disubstituted ester containing a carbonyl group in the β-position with hydrazine, as represented below:



According to this equation, R, R' and R'' have the same meaning as indicated above, that is, R and R' may be the same or different and may be either an alkyl group containing up to four carbon atoms or an aryl group, and R'' may be hydrogen or a low-molecular-weight alkyl group. It is also possible that R and R' are the same.

The synthesis of the compounds of this invention offered considerable difficulties. In Karrer "Organic Chemistry" (Elsevier Publishing Company), 4th edition (1950), it is stated on page 798:

"A very general synthesis of pyrazolone compounds consists in the action of hydrazine or hydrazine derivatives on esters of β-ketonic acids. If formyl acetic ester is used in place of the latter, the parent substance, the simplest pyrazolone, is formed."

In spite of the statement found in Karrer and in spite of the fact that the literature shows many examples of pyrazolone synthesis from phenylhydrazine and substituted acetoacetic esters, when this basic reaction was applied to the synthesis of the compounds of this invention, using hydrazine and disubstituted β-keto- or β-formyl

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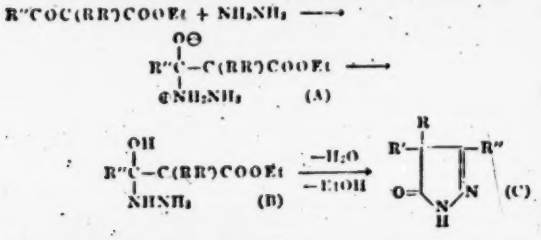
esters, the reaction was satisfactory only with the lower members of the series. For instance, 3,4,4-trimethyl pyrazolone was satisfactorily prepared from dimethyl acetoacetic ester and hydrazine, but the reaction failed when applied to the dibutyl acetoacetic ester. Essentially, the reaction is an addition of hydrazine to the carbonyl group, complicated by the basic character of hydrazine, which is a stronger base than phenylhydrazine, the lack of enolization in the ester component because the presence of two substituents in the α-position and the relatively higher molecular weight of the two substituents, that is, the butyl groups instead of methyl groups. The lack of enolization in the ester component is responsible for the difficulty in the formation of the ester-hydrazine transition complex, represented below by Formula A



The high basicity of hydrazine is expected to make the proton transfer from this transition complex A to the compound shown by B more difficult than in the corresponding complex, where phenylhydrazine is involved. Obviously, the equilibrium is not in favor of the hydrazone formation, and for the pyrazolone synthesis which involves a further cyclodehydration step to give C. The above mentioned theoretical considerations led to the adoption of the following method. It was found that the reaction proceeds satisfactorily by allowing equivalent amounts of hydrazine and the α-disubstituted β-keto or β-formyl ester to react overnight after adjusting the pH to 5, under conditions which provide for the removal of the water formed in the reaction. Thus, decrease of basicity and shifting the equilibrium in favor of the pyrazolone by elimination of the water formed proved very advantageous.

The reaction may be conveniently carried out by placing molar equivalents of hydrazine and of the ester component, preferably in a solvent, in a flask provided with a Soxlet extraction apparatus and placing a dehydrating agent in the thimble of the Soxlet extraction apparatus. Calcium oxide and barium oxide are suitable dehydrating agents, but other dehydrating agents, such as magnesium sulfate and calcium sulfate, may be used. The amount of the dehydrating agent should be sufficient to absorb all the water formed in the reaction, but an excess is preferable.

Obviously, any technique, which allows for the removal of water, is satisfactory, although the procedure comprising refluxing in a Soxlet apparatus with calcium oxide represents the preferred embodiment of the invention. Ethanol is a suitable solvent, but other solvents inert to the reactants may be used.

The method has general application for the synthesis of pyrazolones containing two relatively high-molecular-weight substituents in the 4-position and characterized by the absence of substituents on the two nitrogen atoms.

The following examples are given for the purpose of illustrating the invention, but it is to be understood that the invention is to be limited only by the appended claims.

EXAMPLE 1

3-Methyl-4,4-Dibutyl-Pyrazolone

5 g. of ethyl dibutyl aceto-acetate, 3.4 g. of 85% hydrazine hydrate were dissolved in 150 ml. ethanol and the pH was adjusted to about 5 by dropwise addition of acetic acid. The solution was refluxed for about 16 hours

in a flask provided with a Soxlet thimble containing 20 g. of calcium oxide. Then the solution was filtered to remove traces of calcium oxide carried over into the flask, concentrated to about 15 ml. and diluted with an equal volume of water. A crop of 3 g. of product having a melting point of 95–100° C. was obtained, which was further purified by recrystallization from benzene and precipitation with petroleum ether (B.P. 70 90° C.). The melting point of the pure product was 102–103° C. *Analysis.*—Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54. Found: C, 68.69; H, 10.62.

The substance showed some anticonvulsant activity, but was more toxic than the 4-phenyl-4-methyl compound described in Example 2.

EXAMPLE 2

4-Methyl-4-Phenyl-5-Pyrazolone

Four and three tenths of a gram of ethyl α-formyl α-methyl phenyl acetate, 3.6 grams of 85% hydrazine hydrate were dissolved in 300 ml. of absolute ethanol, and the solution was brought to pH 5 by dropwise addition of acetic acid. The solution was placed in a flask provided with a Soxlet apparatus, and 40 grams of calcium oxide were placed in the thimble. After refluxing for about 17 hours, the solution was filtered, concentrated to about 25 ml. and diluted with an equal volume of water. The crude product, 2.3 grams, recrystallized from heptane and acetone, gave a crop of 1.6 grams of melting point 98–101° C.

Extraction with heptane and concentration of the heptane solution raised the melting point to 99–101° C. *Analysis.*—Calcd. for $C_{10}H_{10}N_2O$: N, 16.08. Found: N, 15.87.

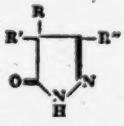
4-methyl-4-phenyl pyrazolone was tested by the minimum electro-shock procedure. The animals were administered the substance orally, and after one hour they were subjected to the direct crurent stimulus, that is, to about three times the current necessary to produce maximum seizures. The dose required to prevent convulsions in one half of the animals tested, in milligrams per kilogram, that is ED_{50}, was 89. The substance had low toxicity, because the NTS_{50}, that is the amount of drug in milligrams per kilogram, which produced neurological toxic symptoms in one half of the animals tested, was 187.

The 3-methyl-4,4-dibutyl pyrazolone, prepared according to Example 1, showed some anticonvulsant activity, but was less active than 4-methyl-4-phenyl-pyrazolone, and more toxic.

It appears that the absence of the methyl group in position 3 and the presence of a phenyl group in position 4 are beneficial for anticonvulsant activity.

I claim:

1. The process of preparing 4,4-disubstituted pyrazolones of formula



wherein each of R and R^1 is a member selected from the group consisting of alkyl of 1 to 4 carbon atoms and phenyl, further characterized by the fact that R may be the same as R^1, and R^{11} is a member selected from the group consisting of hydrogen and lower alkyl, which comprises the steps of adjusting to about 5 the pH of an ethanolic solution of a compound of formula $R^{11}COC(RR^1)COOR^{111}$, wherein R, R^1 and R^{11} have the same meaning as above and R^{111}, is lower alkyl, and the equivalent amount of hydrazine hydrate, refluxing said solution in a flask provided with a Soxlet thimble, said thimble containing a dehydrating agent which is a member selected from the group consisting of CaC, BaO, $MgSO_4$, Na_2SO_4 and anhydrous K_2CO_3, continuing refluxing until all the water formed is removed, and isolating said 4,4-disubstituted pyrazolone from the reaction mixture.

2. The process according to claim 1, wherein said dehydrating agent is CaO in amount exceeding the theoretical amount required to remove the water formed in the reaction.

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